0332

Transcriptomic correlates of HIV reservoir size during antiretroviral therapy

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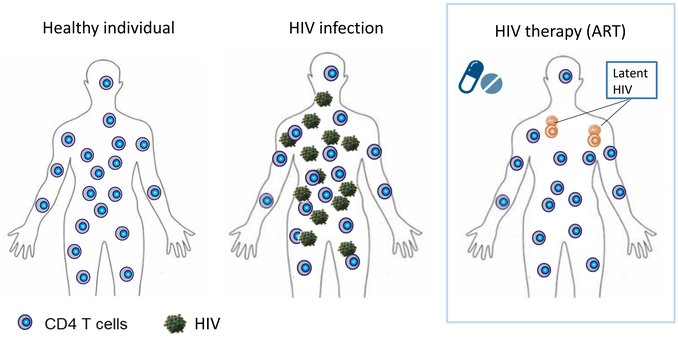
Background

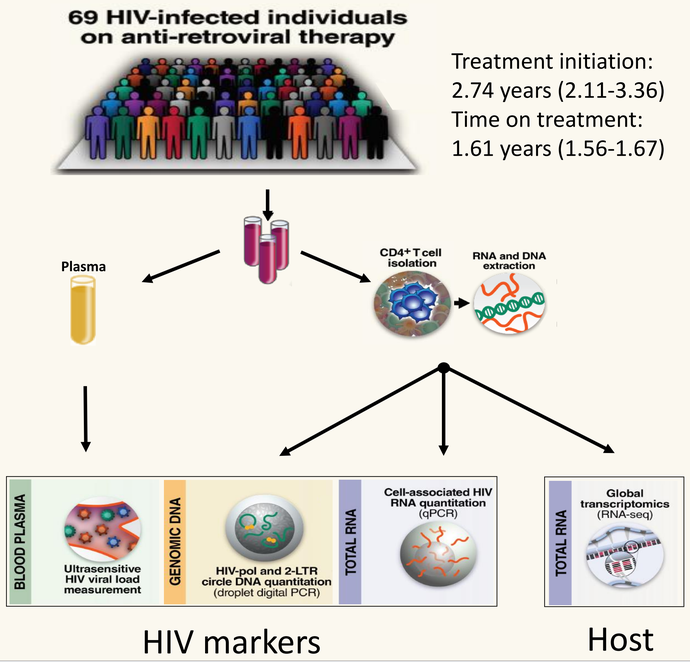


- HIV is an **intracellular pathogen** that **hijacks** the **cellular machinery**
- HIV causes a **persistent infection** under antiretroviral treatment
- Clues for HIV cure approaches lay In the **transcriptome** of **HIV infected cells**

Goal

Examine transcriptome of CD4 T cells in search of host gene expression signatures involved in HIV persistence

Methods

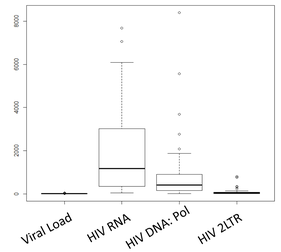


Results

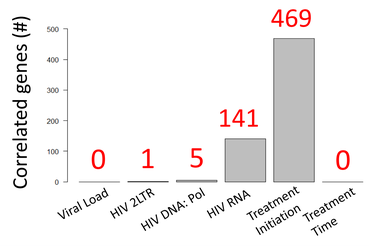
HIV patient characteristics and quantification of HIV markers

	Mean (CI)
Viral load	0.24 (0.17-0.31)
TxInitiation (Years)	2.74 (2.11-3.36)
TxTime (Years)	1.61 (1.56-1.67)
HIV RNA	1906.22 (1436.81-2375.63)
HIV DNA: Pol	807.17(492.07-1122.27)
HIV DNA: 2 LTR	94.10 (54.21-133.99)

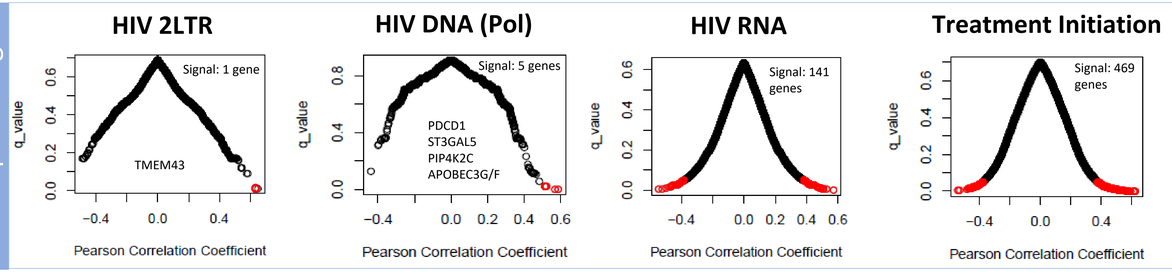
Viral load: log(copies)/mL plasma
HIV RNA, DNA & 2LTR: copies/10^6 PBMCs



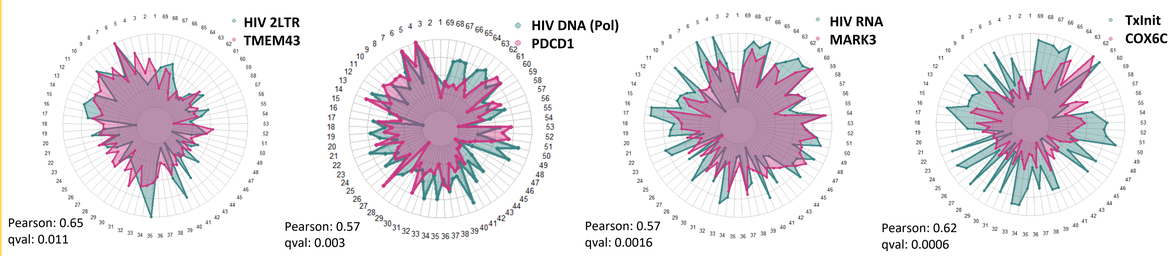
Transcriptome correlates per marker



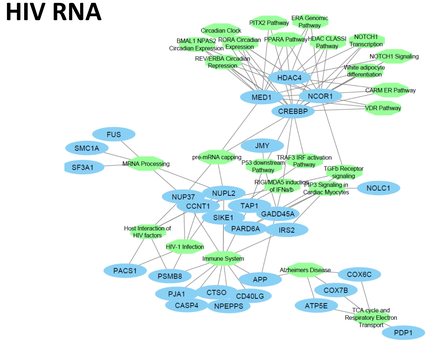
Transcriptome signal



Top correlated gene



Gene Set Enrichment Analysis



Gene Set Name	overlap (#)	k/K	p-value	FDR q-value	geneset(#)
REACTOME_IMMUNE_SYSTEM	13	0.01	4.41E-07	5.86E-04	933
BIOCARTA_VDR_PATHWAY	3	0.25	2.97E-06	1.97E-03	12
REACTOME_HOST_INTERACTIONS_OF_HIV_FACTORS	5	0.04	1.82E-05	5.08E-03	132
SIG_PIP3_SIGNALING_IN_CARDIAC_MYOCTES	4	0.06	2.20E-05	5.08E-03	67
REACTOME_CIRCADIAN_REPRESSION_OF_EXPRESSION_BY_REV_ERBA	3	0.13	2.34E-05	5.08E-03	23
REACTOME_PROCESSING_OF_CAPPED_INTRON_CONTAINING_PRE_MRNA	5	0.04	2.41E-05	5.08E-03	140
REACTOME_RORA_ACTIVATES_CIRCADIAN_EXPRESSION	3	0.13	2.67E-05	5.08E-03	24
REACTOME_MRNA_PROCESSING	5	0.03	4.71E-05	7.83E-03	161
BIOCARTA_CARM_ER_PATHWAY	3	0.09	8.48E-05	1.23E-02	35
REACTOME_BMAL1_CLOCK_NPAS2_ACTIVATES_CIRCADIAN_EXPRESSION	3	0.08	9.24E-05	1.23E-02	36
REACTOME_HIV_INFECTION	5	0.02	1.54E-04	1.86E-02	207
REACTOME_NOTCH1_INTRACELLULAR_DOMAIN_REGULATES_TRANSCRIPTION	3	0.07	1.70E-04	2.14E-02	46
REACTOME_CIRCADIAN_CLOCK	3	0.06	2.94E-04	3.01E-02	53
PID_P53_DOWNSTREAM_PATHWAY	4	0.03	3.54E-04	3.28E-02	137
BIOCARTA_PPARA_PATHWAY	3	0.05	3.84E-04	3.28E-02	58
REACTOME_TCA_CYCLE_AND_RESPIRATORY_ELECTRON_TRANSPORT	4	0.03	3.94E-04	3.28E-02	141
REACTOME_SIGNALING_BY_TGF_BETA_RECEPTOR_COMPLEX	3	0.05	4.90E-04	3.73E-02	63
REACTOME_TRAF3_DEPENDENT_IRF_ACTIVATION_PATHWAY	2	0.14	5.16E-04	3.73E-02	14
PID_ERA_GENOMIC_PATHWAY	3	0.05	5.37E-04	3.73E-02	65
PID_HDAC_CLASS1_PATHWAY	3	0.05	5.62E-04	3.73E-02	66
BIOCARTA_PITX2_PATHWAY	2	0.13	5.95E-04	3.76E-02	15
REACTOME_SIGNALING_BY_NOTCH1	3	0.04	6.67E-04	4.03E-02	70
REACTOME_TRANSCRIPTIONAL_REGULATION_OF_WHITE_ADIPOCYTE_DIFFERENTIATION	3	0.04	7.24E-04	4.14E-02	72
REACTOME_RIG_I_MDA5_MEDIATED_INDUCTION_OF_IFN_ALPHA_BETA_PATHWAYS	3	0.04	7.54E-04	4.14E-02	73
KEGG_ALZHEIMERS_DISEASE	4	0.02	7.78E-04	4.14E-02	169

Correlation Analysis

- Genes with RNAseq counts >10 Reads Per Kilobase Million across samples were analyzed: 9543 genes expressed
- CD4+ T cell transcriptomes were correlated with reservoir markers and ART initiation timing in a guilt-by-association manner and involved the construction of correlation matrices (Pearson) with subsequent gene set enrichment analysis
- Significance was determined using a False Discovery Rate adjusted p-value (q-value) cutoff of 0.05. Gene sets were retrieved from the molecular signature databases: BIOCARTA, KEGG and REACTOME

Conclusion

- This study reveals associations between host genetic pathways and HIV persistence
- Especially **HIV RNA levels** were correlated with following pathways:
  Notch, p53 pathway, RIG-I and EDG1-induced **T cell exhaustion**
- **HIV DNA levels** correlated with PDCD1 and ST3GAL5 genes which indicate **clonal proliferation** as hallmark of HIV persistence
- **Treatment initiation** was associated with pathways useful for immunotherapy: p53, mTOR

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